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A Comparative Study of Dialkylboron Chlorides and Triflates for
the Enolization of Ketones. The Controlled Stereospecific Synthesis
of Either [E]- or [Z]-Enol Borinates

by

Herbert C. Brown, Bakthan Singaram, Raman K. Bakshi,
Paul K. Pandiarajan and Raj K. Dhar

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Purdue University
H. C. Brown and R. B. Wetherill Laboratories of Chemistry
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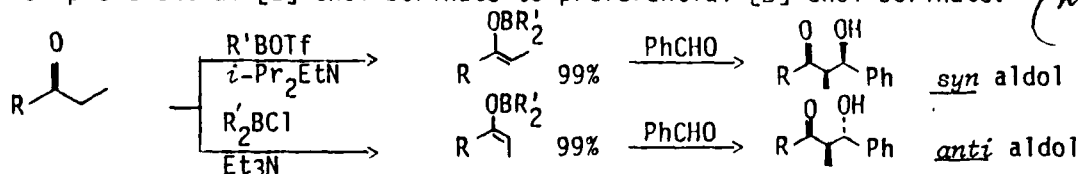
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A COMPARATIVE STUDY OF DIALKYLBORON CHLORIDES AND TRIFLATES FOR THE ENOLIZATION OF KETONES. THE CONTROLLED STEREOSPECIFIC SYNTHESIS OF EITHER [E]- OR [Z]-ENOL BORINATES. Herbert C. Brown, Bakthan Singaram, Raman K. Bakshi, Paul K. Pandiarajan and Raj K. Dhar, H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907

The ready synthesis and ease of handling of dialkylboron chlorides, R_2BCl , as compared to the corresponding triflates, R_2BOTf , give the chlorides a significant advantage as reagents to achieve the conversion of ketones into enol borinates quantitatively. A systematic study, in the case of two representative ketones, propiophenone and diethyl ketone, of the effect of the steric requirement of the R group ($R_2 = 9\text{-BBN}$ vs. Chx_2), the amine, Et_3N vs. $i\text{-}Pr_2EtN$, and the leaving group, Cl vs. OTf , has revealed a controlled shift from preferential [Z]-enol borinate to preferential [E]-enol borinate.



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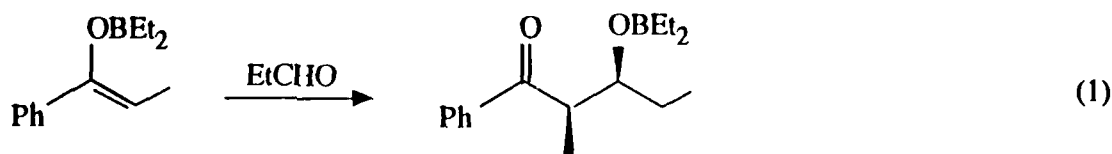
A Comparative Study of Dialkylboron Chlorides and Triflates for the Enolization of Ketones. The Controlled Stereospecific Synthesis of Either [E]- or [Z]-Enol Borinates

Herbert C. Brown, Bakthan Singaram, Raman K. Bakshi, Paul K. Pandiarajan and Raj K. Dhar

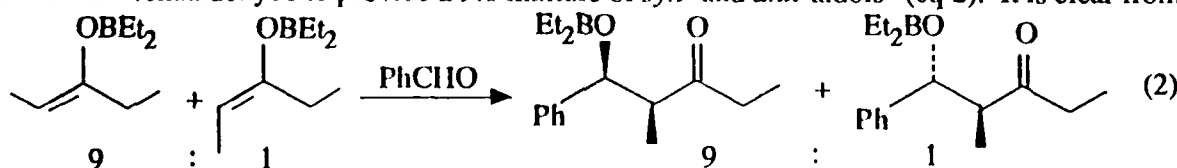
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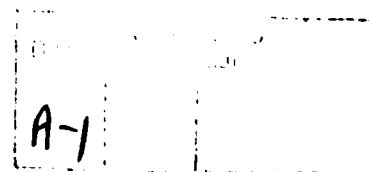
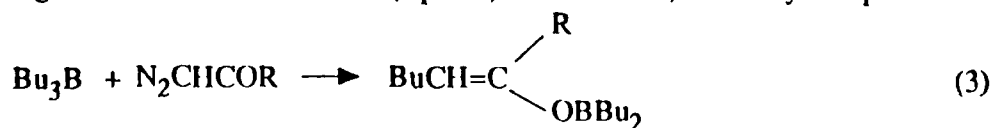
Ketone enolates are useful intermediates in organic synthesis. Indeed, their nucleophilic properties are intensively applied to form carbon-carbon bonds in a number of important reactions.^{1,2} Consequently, considerable attention has been paid in the past decade to the generation of enol borinates by the reaction of ketones with tertiary amines and boron compounds containing good leaving groups. It is now well established that highly diastereoselective kinetic aldol condensations can be achieved by incorporating into the ketone metal enolate the appropriate steric control.^{3,4} Further, it is now recognized that for a given carbonyl compound, boron enolates are normally more stereoselective than other metal enolates. For example, it was shown by Fenzl and Köster that the [Z]-diethylboron enolate of propiophenone reacts with propionaldehyde to give only the *syn* aldol (eq 1).⁵

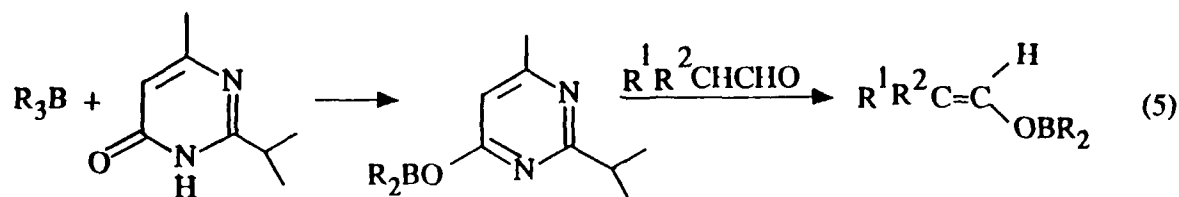
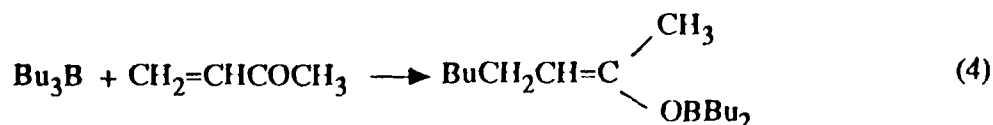


It was also shown that a 9:1 mixture of [Z]- and [E]-enolates, obtained from 3-pentanone, reacts with benzaldehyde to provide a 9:1 mixture of *syn*- and *anti*-aldols⁵ (eq 2). It is clear from



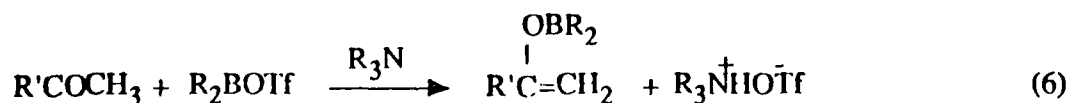
these results that the boron enolate additions are highly stereoselective, with [Z]-enolates giving *syn* aldols, and the [E]-enolates giving *anti* aldols. A number of published methods have been described for the generation of enol borinates (eqs 3-5).^{6,7} However, relatively few procedures





have been developed for the generation of enol boronates directly from the ketones.

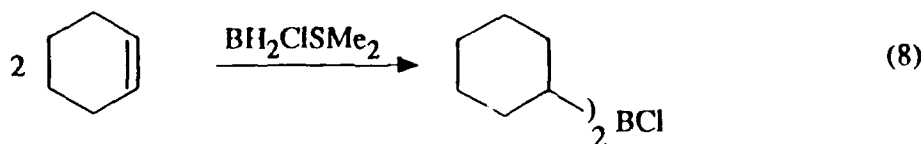
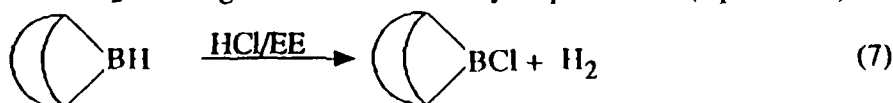
In 1976 Mukaiyama discovered that enol borinates can be easily prepared from ketones by treating with dialkylboron triflates (R_2BOTf) and a tertiary amine (eq 6).⁸ This procedure has been



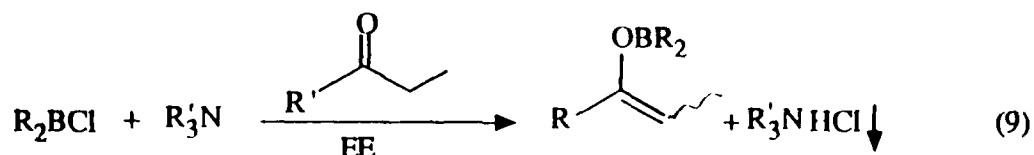
widely used for the stereoselective generation of enol borinates from ketones. However, there are some drawbacks in this procedure. Dialkylboron triflates have limited stability. Consequently, it is usually recommended that they be prepared fresh before use. Moreover, the use of R_2BOTf in most cases leads to the formation of *[Z]*-enolates and ultimately to the *syn*-aldols.⁹ Only for a few special ketones has it been possible to generate the *[E]*-enolates with the dialkylboron triflates.^{10,11}

Accordingly, we undertook a detailed study of the reaction of selected R_2BCl with ketones in the presence of tertiary amines. We discovered that these derivatives can be used in place of the triflates and an unexpected bonus from these studies was the discovery that these R_2BCl reagents permit the synthesis of the previously unavailable *[E]*-enolates.

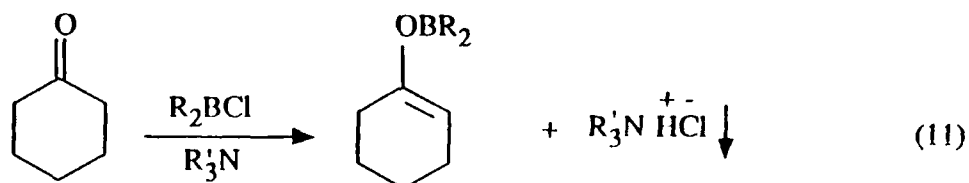
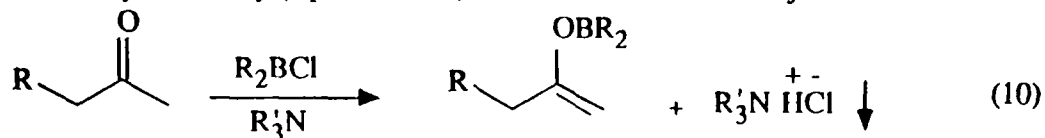
The preparation of the R_2BCl reagents used in this study is quite facile (eqs 7 and 8).^{12,13}



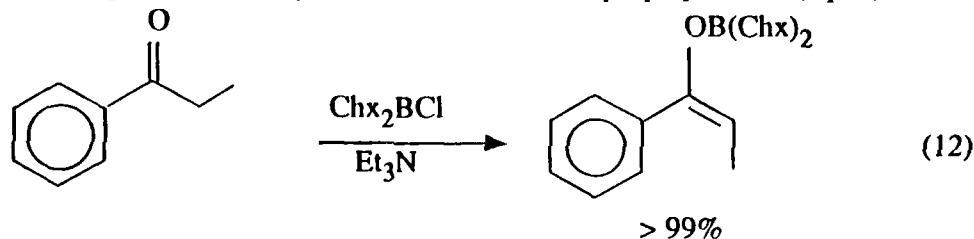
Treatment of the R_2BCl in diethyl ether (EE) at 0°C with tertiary amine, followed by the addition of the carbonyl compound, produces the corresponding enol borinates instantaneously and quantitatively (eq 9). This method appears to be general and it proved possible to enolize a wide



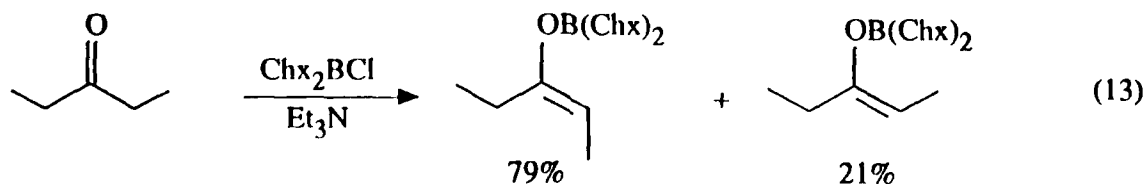
variety of ketones very efficiently (eqs 10 and 11). These enolates were subjected to aldol reaction



with benzaldehyde at -78°C (2 h) and the ratio of *syn*- to *anti*-aldol products determined in each case. Additionally, in the case of propiophenone, it proved possible to determine the [*E*] and [*Z*]-enolate ratio directly by ^1H NMR spectral analysis. We were pleasantly surprised to find that dicyclohexylchloroborane gave exclusively [*E*]-enol borinate from propiophenone (eq 12).



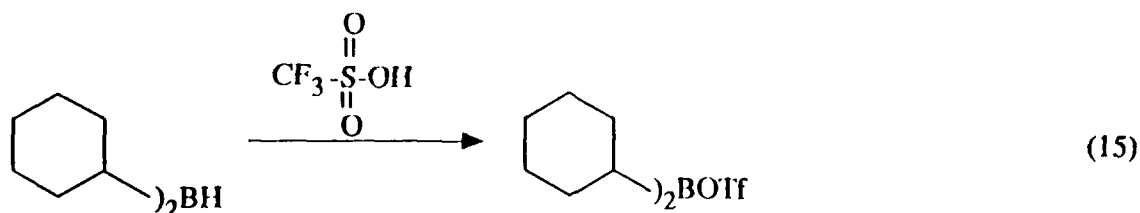
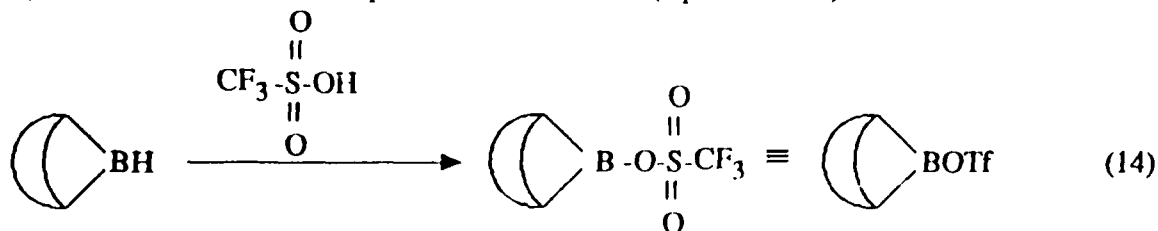
To our knowledge, this is the first successful preparation of pure [*E*]-enolate from propiophenone. Contrary to general belief, this [*E*]-enolate reacts stereospecifically with aldehyde to give *anti*-aldol product exclusively. Encouraged by this result, we checked the possibilities of generating [*E*]-enolate from diethyl ketone. In the case of diethyl ketone, the reaction also yielded the [*E*]-enolate predominantly (eq 13).



These results differ from those reported in the literature for enolization of propiophenone and diethyl ketone using R_2BOTf .

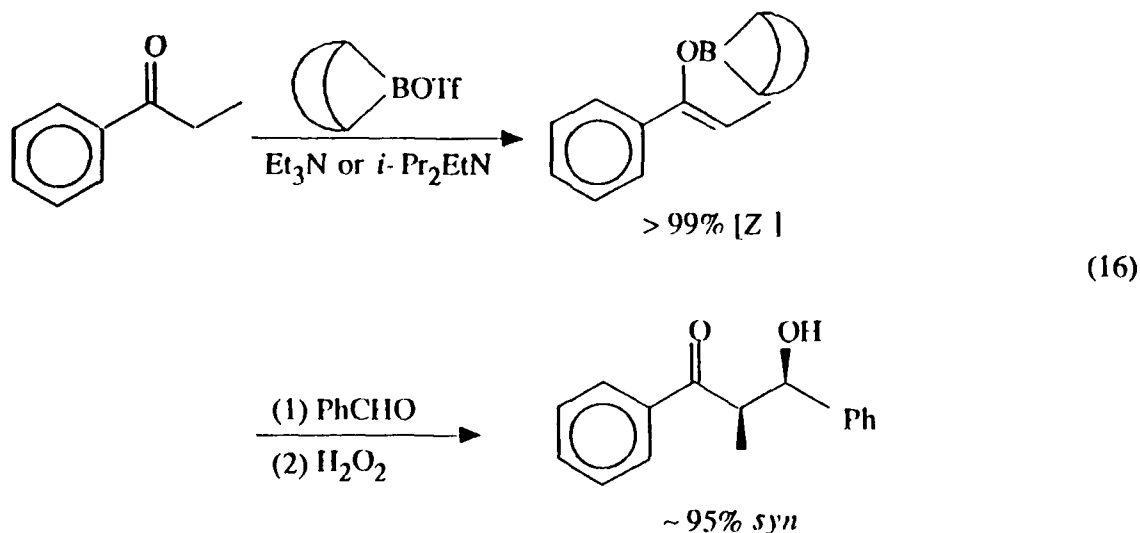
In order to compare the effect of the leaving group on boron, we carried out a systematic study of the enolization of propiophenone and diethyl ketone using two different R_2BX ($B-X-9-$

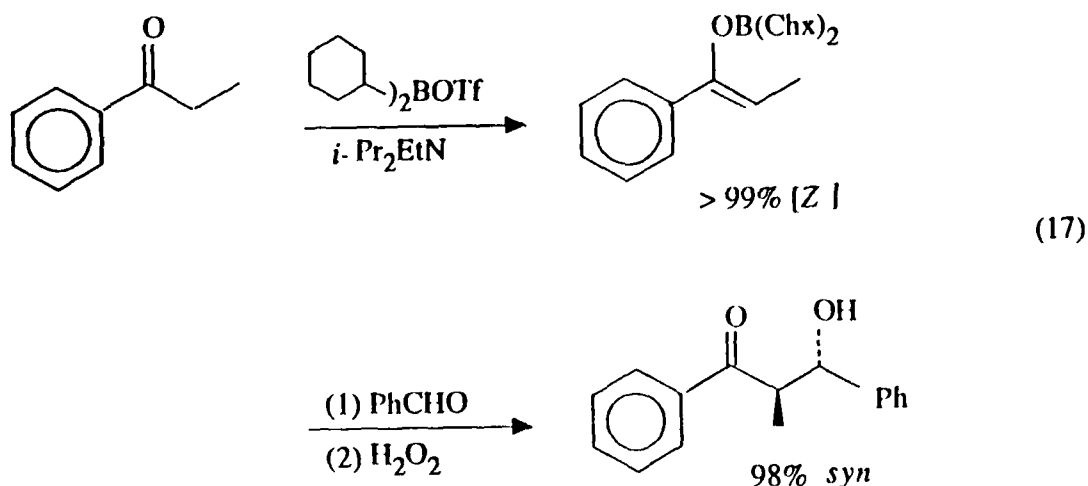
BBN and Chx_2BX ; $\text{X} = \text{Cl}$ or OTf) and two different amines, Et_3N and $i\text{-Pr}_2\text{EtN}$. The preparation of R_2BOTf was carried out as reported in the literature (eqs 14 and 15).⁸



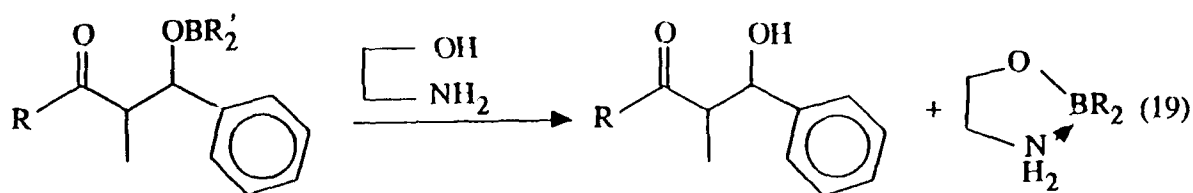
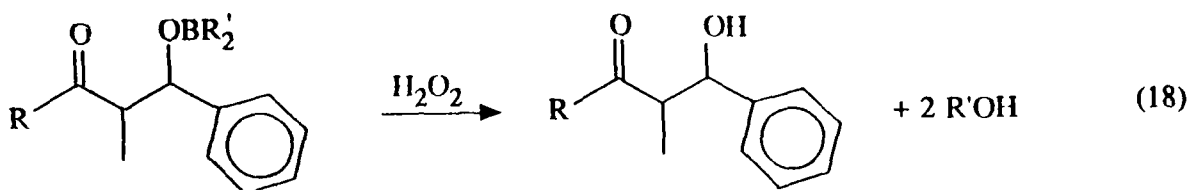
These results revealed that the use of R_2BCl and Et_3N gives *syn*-aldol from [Z]-enolate or *anti*-aldol from [E]-enolate, with the ratio varying with the steric requirements of the alkyl groups on boron. Use of $i\text{-Pr}_2\text{NEt}$ for enolization leads only to the formation of *syn*-aldol. Use of the corresponding triflates also lead to the formation of *syn*-aldol, irrespective of the amine used (Table I).

It is seen that the stereochemical outcome of the reaction depends both on the nature of the leaving group and the steric requirements of R_2B , as well as on the steric requirement of the amine used. The effect of varying the amine and the alkyl groups on boron are more significant in the case of R_2BCl . The corresponding triflates always give [Z]-enolate (*syn*-aldol) predominantly, irrespective of the nature of the alkyl group (eqs 16 and 17).

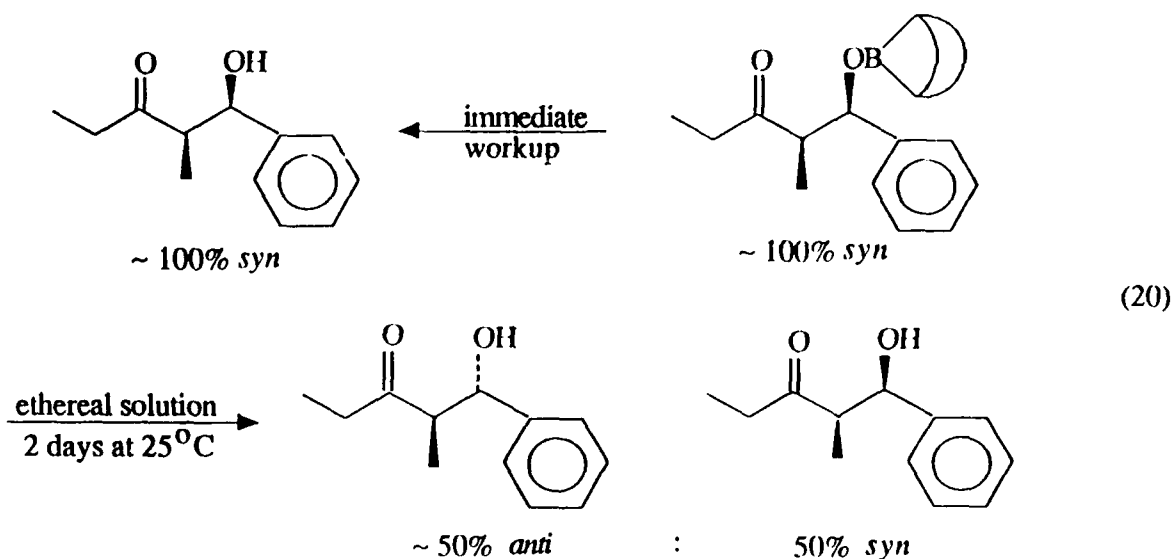




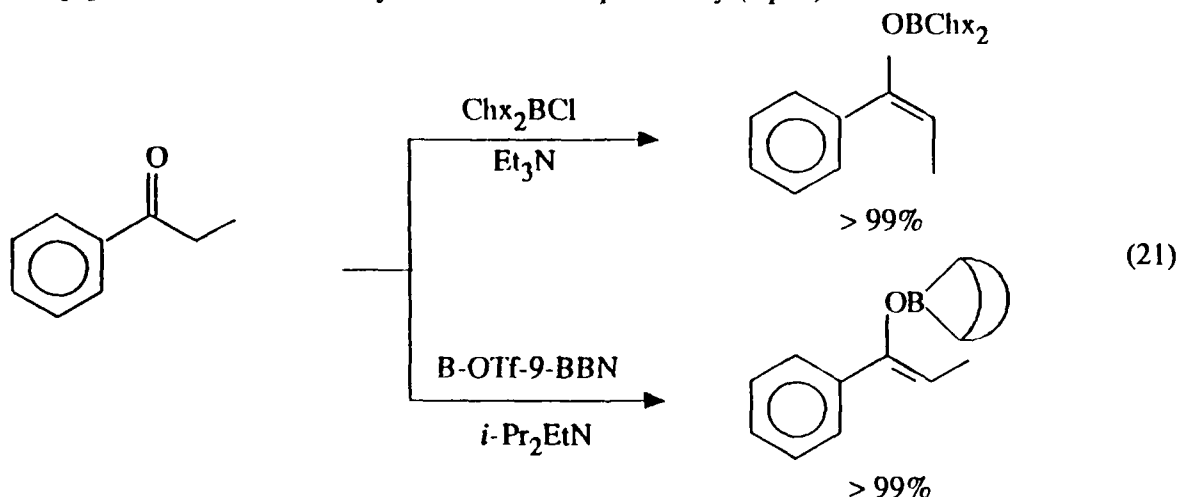
Two procedures were developed to remove the boron moiety from the boron-aldolate: 1) oxidative workup and 2) ethanolamine complexation workup (eqs 18 and 19).



Both of these procedures can be employed to prepare aldol products without significant isomerization or decomposition. Further, it was observed that the [E]-enolates are thermodynamically less stable and undergo isomerization with time to the more stable [Z]-enolate. On the other hand, syn-aldolates tend to isomerize to the *anti* products (eq 20).



By an appropriate choice of the dialkylborane derivative and the tertiary amine, either a [Z]- or an [E]-enol borinate can be synthesized stereospecifically (eq 21).



This is the first time that high *anti* selectivity or [E]-enolate formation has been achieved successfully for PhCOEt and EtCOEt. This study has demonstrated that dialkylchloroborane can be effectively used for enolization of a variety of ketones. This, combined with the fact that dialkylchloroboranes are readily synthesized and are very stable, makes the methodology described here a valuable contribution to the aldol reaction.

Conclusion

The R_2BCl reagents provide a convenient alternative to the R_2BOTf reagents for converting ketones into the corresponding enol borinates. The formation of [E]-enolate over [Z]-enolate is favored by the following: a) use of R_2BCl vs. R_2BOTf ; b) use of Et_3N over $i-Pr_2EtN$; c) use of R_2B of larger steric requirements over R_2B with smaller steric requirements.

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Table I. Enolization of Propiophenone and Diethyl Ketone Using R₂BX^a

reagent R ₂ BX	amine R ₃ N	Z:E ^c	propiophenone syn:anti ^d	diethyl ketone syn:anti ^d
B-Cl-9-BBN	Et ₃ N	52:48 65:35 ^b	60:40	~ 100:0
B-OTf-9-BBN	<i>i</i> -Pr ₂ EtN	100:0 ^b	95:5	~ 100:0
	Et ₃ N	100:0	93:7	~ 100:0
	<i>i</i> -Pr ₂ EtN	100:0	95:5	~ 100:0
Chx ₂ BCl	NEt ₂	0:100	5:95	21:79
	<i>i</i> -Pr ₂ EtN	51:49		72:28
Chx ₂ BOTf	Et ₃ N	67:33		80:20
	<i>i</i> -Pr ₂ EtN	100:0	98:2	93:7

^aEnolization at 0°C (2 h), except where otherwise noted. ^bEnolization at 25°C. ^cDirect measurement of Z:E ratios of enol borinates by PMR. ^dMeasurement of the diastereoselection achieved in the benzaldehyde aldol product.